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<p>(21) International Application Number: PCT/GB97/00420 (22) International Filing Date: 14 February 1997 (14.02.97) (30) Priority Data: 9603146.3 15 February 1996 (15.02.96) GB (71) Applicant (for all designated States except US): INNOVATIVE TECHNOLOGIES LIMITED [GB/GB]; Road Three, Winsford Industrial Estate, Winsford, Cheshire CW7 3PD (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): GILDING, Denis, Keith [GB/GB]; Nepenthe, Winsford Road, Wettehall, Winsford, Cheshire CW7 4DL (GB). AL-LAMEE, Kadem, Gayad [GB/GB]; Innovative Technologies Limited, Road Three, Winsford Industrial Estate, Winsford, Cheshire CW7 3PD (GB). (74) Agent: ATKINSON, Peter, Birch; Marks & Clerk, Sussex House, 83-85 Mosley Street, Manchester M2 3LG (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.</p>
<p>(54) Title: HYDROGELS (57) Abstract A hydrogel comprises a cross-linked form of at least one water soluble polysaccharide selected from (i) polysaccharides comprised of galactomannan residues, or (ii) chitosan or derivatives thereof.</p>		

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HYDROGELS

The present invention relates to hydrogels which are intended particularly, but not exclusively, for use as wound dressings.

Hydrogels are water-swollen, three dimensionally cross-linked hydrophilic polymers which are typically formed by cross-linking the polymer under aqueous conditions using a low amount of cross-linking agent so that a water-swollen, cross-linked polymer is produced. The amount of cross-linking agent should not be too high otherwise the degree of cross-linking achieved will not allow the water swelling of the polymer necessary to produce the hydrogel. The cross-links are usually either covalent or ionic bonds.

Hydrogels are used as wound dressings and have a number of advantages which render them suitable for this purpose. In particular, they

- (1) are particularly effective at promoting hydration, and therefore wound debridement;
- (2) have the ability to take up significant quantities of exudate in the management of more heavily exuding wounds;
- (3) are very thick putty-like, tacky and spreadable, and may be used for treatment of open cavity wounds such as pressure ulcers and leg ulcers;
- (4) retain their physical form as they absorb fluid; and
- (5) can (if required) also form carriers for antimicrobial agent or growth factors or any other biologically active molecules in order to speed up the healing process.

Commercially available hydrogels do however suffer from a number of disadvantages. In particular they do not always retain their physical form for a sufficiently long period of time and as such do not absorb fluid for a sufficient time.

It is an object of the present invention to provide hydrogels which obviate or mitigate the abovementioned disadvantages.

According to the present invention there is provided a hydrogel comprising a cross-linked form of at least one water soluble polysaccharide selected from

- (i) polysaccharides comprised of galactomannan residues, or
- (ii) chitosan or derivatives thereof.

Hydrogels in accordance with the invention are derived from the biocompatible and biodegradable polysaccharides identified under (i)-(ii) and may be used as either amorphous gels or sheet dressings. The hydrogels comprised of the cross-linked form of (i) and/or (ii) may optionally further comprise a cross-linked form of at least one water soluble polysaccharide selected from

- (iii) pectin, pectic acid or pectate.

Hydrogels in accordance with the invention are capable, when used as wound dressings, of retaining their physical form and absorbing fluid over substantial periods of time when used in a hydrated wound. They are also capable of taking up larger quantities of fluid than current commercial hydrogels. The hydrogels of the invention also have the advantage being able to donate significant quantities of fluid to a dry wound.

One class of hydrogels (i) in accordance with the invention are those derived from polysaccharides comprised of galactomannan residues (galactomannan is a polymer of D-galactose and D-mannose). Examples of polymers comprising galactomannan residues which may be used in accordance with the invention are those derived from seed gums. e.g. guar gum and locust bean gum.

Hydrogels may be produced from the polysaccharide (i) by effecting cross-linking thereof with a borate ion e.g. provided by an alkali metal borate (e.g. sodium borate). It is however also possible to use transition metal ions such as titanium although borate is preferred.

Hydrogels may be produced from the polysaccharide (i) by admixed with water and the desired cross-linking agent. The reaction is preferably effected at a pH less than 9, preferably 6 to 8, ideally about pH = 7. Preferably the amount of the polysaccharide (i) is 1% to 6% w/v of the admixture, more preferably 1% to 5% on the same basis, e.g. about 4% w/v. Gels produced by this method may be either spreadable or "rubbery" depending on the concentration of the cross-linking agent used. If it is desired to produce a spreadable product, then it is preferred to use at most about 0.01% w/v of cross-linking agent. If it is desired to produce a sheet hydrogel then the amount of the cross-linking agent may be up to about 0.2% w/v.

Hydrogels produced as described above from the polysaccharide (i) show no thermal degradation when autoclaved at 120°C over 6 hours. This is believed to be due to the use of borate as the cross-linking agent.

Hydrogels produced from polysaccharides (ii) may be obtained in a number of ways which will be described with specific reference to chitosan although these methods may be applied to chitosan derivatives such as carboxymethyl chitosan.

Firstly, chitosan may be cross-linked using a dialdehyde which reacts with amino groups on the chitosan molecule. The dialdehyde is preferably of the formula $\text{OHC}(\text{CH}_2)_n\text{CHO}$ where n is 1 to 5, most preferably 3. This cross-linking reaction is preferably effected in an acidic solution (e.g. at a pH of about 4) of the chitosan. Typically the amount of chitosan will be used in the range 1% to 6% w/v (e.g. about 3% w/v) and the dialdehyde will be used in the range 0.0005 to 0.01% w/v (e.g. about 0.001%). This method is particularly suitable for the production of hydrogels in sheet form.

Secondly, chitosan may be cross-linked using a dicarboxylic acid, preferably using a carbodiimide as an activator. It is particularly preferred that the dicarboxylic acid is a polyalkylene glycol dicarboxylic acid (preferred molecular weight range 200 to 2,000), most preferably a polyethylene glycol dicarboxylic acid. The cross-linking proceeds via reaction of the carboxylic acid groups (on the cross-linking agent) with amino groups on the chitosan with the aid of a water soluble carbodiimide so that the polysaccharide chains are cross-linked by diamide linkages. Preferably the amount of chitosan is 1% to 6% w/v and the amount of dicarboxylic acid is 1 to 2% w/v. Such compositions are suitable as amorphous hydrogels.

Thirdly, the chitosan may be reacted with a polymer having carboxylic acid groups along its chain to yield a modified chitosan having carboxylic pendant groups

(attached to the "polymer" backbone). The reaction is preferably effected in the presence of a carbodiimide. A suitable co-polymer is N-vinyl pyrrolidone acrylic acid (NVP-AA). This modified chitosan may then be cross-linked using a multivalent ion (preferably calcium) to form a hydrogel. Preferably such a hydrogel comprises 2%-6% w/v chitosan or derivative thereof, 1% to 3% w/v N-vinyl pyrrolidone carboxylic acid, copolymer, and 0.02% to 2% w/v calcium).

All of the above-described hydrogels based on the cross-linked form of polysaccharides (i) or (ii) may further comprise a cross-linked form of a polysaccharide (iii) (i.e. pectin, pectic acid or pectate) which has preferably been cross-linked with a multivalent cation, preferably calcium. The amount of polysaccharide (iii) in the hydrogel is preferably in the range 2 to 4% w/v and multivalent cation is present in an amount up to 0.2% w/v, e.g. 0.02% w/v.

A particularly preferred embodiment of the invention relates to a gel which is comprised of cross-linked polysaccharides (i) and (iii). In the gel, the former may be cross-linked by borate and the latter cross-linked by a multivalent ion.

Incorporation of a cross-linked polymer (iii) in a gel comprised of cross-linked polysaccharide (i) and/or (ii) improves the adhesion of the latter in wounds as well as to increase the exudate up-take in the wound by the gel.

All of the above described hydrogels may, with advantage, incorporate a polyhydric alcohol (e.g. in an amount up to 20% w/v) as a plasticiser and stabiliser to improve the shelf-life of the gel. The preferred polyhydric alcohol is propylene glycol

The invention is illustrated by the accompanying drawings, in which:

Fig. 1 illustrates a part of the structure of guar gum:

Fig. 2 illustrates the cross-linking of guar gum with a borate:

Fig. 3 illustrates a hydrogel comprised of a mixture of (a) guar gum (chain 1) cross-linked with borate) and (b) pectic acid (chain 2) cross-linked with calcium ions;

Fig. 4 illustrates the structure of chitosan;

Fig. 5 illustrates the cross-linking of chitosan with glutaraldehyde; and

Fig. 6 illustrates chitosan modified by reaction with a N-vinylpyrrolidone acrylic acid co-polymer, the modified chitosan then being cross-linked by means of calcium ions which react with free carboxylic acid groups on the NVP-AA co-polymer chain.

Figs. 1 and 2 are generally self-explanatory, the former showing a portion of the structure of guar gum and the latter showing the manner in which guar gum chains are cross-linked by borate ions.

Referring now to Fig. 3, there is schematically illustrated a product which comprises cross-linked guar gum and cross-linked pectic acid. More particularly, the guar gum chain is represented by reference numeral 1 and is shown to be cross-linked by borate ions (in the manner depicted in Fig. 2). The pectic acid chain is depicted by reference numeral 2 and is shown to be cross-linked by calcium ions.

Fig. 4 illustrates a portion of the structure of chitosan whereas Fig. 5 illustrates the cross-linking thereof using the dialdehyde $\text{OCH}(\text{CH}_2)_3\text{CHO}$, the cross-linking being effected by reaction between amino groups of chitosan and the aldehyde groups of the cross-linking agent.

Referring now to Fig. 6, there is illustrated the reaction product of chitosan with N-vinylpyrrolidone acrylic acid co-polymer. More particularly, a portion of the carboxylic acid groups on the co-polymer react with amino groups of the chitosan (to produce amide linkages) to produce a modified chitosan have free carboxylic acid groups on the polymer residue. The modified chitosan may then be cross-linked using calcium ions as shown.

The invention is further illustrated by the following non-limiting Examples.

Example 1

Guar gum (4g) was dissolved in 81 ml distilled water and 15 ml propylene glycol. The mixture was then homogenised with the aid of a high shear mixer. The resulting product is a smooth and highly viscose mixture which was then cross-linked after the addition of 0.01g sodium tetraborate anhydrous (borax) to produce a hydrogel. This hydrogel is cream coloured, thick, and paste-like. It was autoclaved at 121 °C for 15 minutes without apparent deterioration of the gel.

Example 2

Guar gum (4g) was dissolved in 59 ml of distilled water containing 15 ml of propylene glycol. Pectic acid (2g) was suspended in 20 ml distilled water and the pH of this mixture was then adjusted with dilute sodium hydroxide to produce homogenise solution. The latter solution was then added to guar gum solution and the two components were mixed well using a high shear mixer. These two carbohydrates

were then cross-linked after the addition of 0.02g of calcium chloride and 0.004g borax respectively. The hydrogel produced by this technique is creamed coloured, thick and paste-like. This gel was autoclaved for 15 minutes at 121 °C without apparent deterioration.

Example 3

Chitosan (3g) was dissolved in 80 ml distilled water containing 1ml acetic acid and 15 ml propylene glycol. The resulting mixture was highly viscous and it was then cross-linked with a solution of polyethylene glycol dicarboxylic acid (0.5 g) and 1-Ethyl-3-(3-Diethyl amino propyl) Carbodiimide (EDC) (0.3 g) in 5ml water. After the addition of the latter solution a hydrogel was formed. This cross-linked gel was clear, thick and spreadable.

Example 4

Chitosan (3g) was dissolved in 70 ml distilled water containing 6ml of 1M HCl and the mixture was then homogenised as described above. A solution of a copolymer of N-vinyl pyrrolidone-acrylic acid (1.8 g) in 15 ml distilled water was activated with EDC (30 mg) for 15 minutes at room temperature before it was added to the chitosan mixture. This reaction was left going for 2 hours at room temperature before the addition of calcium chloride (0.02 g) to form cross-linked hydrogel. Propylene glycol (15 ml) was then added and the components were mixed well. The

product was creamed coloured, thick, sticky and it was autoclaved without any apparent deterioration.

Example 5

In this experiment 3 g of chitosan were dissolved in 81 ml water containing 1 ml of acetic acid and 15 ml of propylene glycol. The mixture was then homogenised with the aid of a high shear mixer. The mixture was then cross-linked with 1 mg of glutaraldehyde to form a gel. The resulting hydrogel was then autoclaved and the colour of the gel became slightly yellow. To avoid the formation of this yellow colour, the gel was reacted further with a reducing agent such as sodium borohydride before autoclaving.

Example 6

Chitosan (3g) was dissolved in 68 ml of distilled water containing 1ml of acetic acid and 15 ml of propylene glycol. The mixture was then homogenised with the aid of a high shear mixer. Pectic acid (2g) was suspended in 11 ml of water and it was dissolved when the pH of the solution was raised to 3 after the addition of diluted sodium hydroxide. The pectic acid solution was then added to chitosan solution and the two polysaccharides mixed very well before they were cross-linked with a divalent ion source (e.g. 0.02g calcium chloride) to form a spreadable gel.

Example 7

Carboxymethylchitosan (5g) was dissolved in 80 ml distilled water containing 15 ml of propylene glycol. The mixture was homogenised as described above and then was cross-linked with a divalent ion source (e.g. 0.024 g of calcium chloride) to form a spreadable gel.

Example 8

A mixture of 4% guar gum, 2% pectic acid, 15% propylene glycol and 79% distilled water was homogenised with aid of high sheer mixture before the cast as a film onto microporous nylon membrane. This film was then cross-linked after immersion into a coagulation bath containing 0.2% calcium chloride and 0.01% borate to form a hydrogel sheet.

CLAIMS

1. A hydrogel comprising a cross-linked form of at least one water soluble polysaccharide selected from
 - (i) polysaccharides comprised of galactomannan residues, or
 - (ii) chitosan or derivatives thereof.
2. A hydrogel as claimed in claim 1 wherein the water soluble polysaccharide is one comprised of galactomannan residues.
3. A hydrogel as claimed in claim 2 wherein the water soluble polysaccharide comprises galactomannan residues and is derived from a seed gum.
4. A hydrogel as claimed in claim 3 wherein the seed gum is guar gum or locust bean gum.
5. A hydrogel as claimed in any one of claims 2 to 4 wherein the polysaccharide is cross-linked with borate ions.
6. A hydrogel as claimed in claim 5 comprising up to 0.2% w/v of borate from which the borate ions are derived.

7. A hydrogel as claimed in claim 6 comprising up to about 0.01% w/v of borate.
8. A hydrogel as claimed in any one of claims 5 to 7 wherein the borate is an alkali metal borate.
9. A hydrogel as claimed in any one of claims 2 to 4 wherein the polysaccharide is cross-linked with transition metal ions.
10. A hydrogel as claimed in any one of claims 2 to 9 comprising 1% to 6% w/v of the polysaccharide.
11. A hydrogel as claimed in claim 10 comprising 1% to 5% w/v of the polysaccharide.
12. A hydrogel as claimed in claim 1 wherein the water soluble polysaccharide is chitosan or a derivative thereof.
13. A hydrogel as claimed in claim 12 wherein the chitosan or derivative thereof is cross-linked with a dialdehyde.
14. A hydrogel as claimed in claim 13 wherein the dialdehyde is of the formula $\text{OHC}(\text{CH}_2)_n\text{CHO}$ where n is 1 to 5, most preferably 3.

15. A hydrogel as claimed in claim 13 or 14 comprising 1% to 6% w/v of the chitosan or derivative thereof and 0.001% to 1% w/v of the dialdehyde.
16. A hydrogel as claimed in claim 12 wherein the chitosan or chitosan derivative is cross-linked with a dicarboxylic acid.
17. A hydrogel as claimed in claim 16 wherein the dicarboxylic acid is a polyalkylene glycol dicarboxylic acid.
18. A hydrogel as claimed in claim 17 wherein the dicarboxylic acid is a polyethylene glycol dicarboxylic acid.
19. A hydrogel as claimed in any one of claims 16 to 18 comprising 1% to 6% w/v of the polysaccharide and 0.5% to 2% of the dicarboxylic acid.
20. A hydrogel as claimed in claim 12 wherein the cross-linking is achieved by reaction of the polysaccharide with a polymer having carboxylic acid groups along its chain to produce a modified polysaccharide having carboxylic pendant groups which are cross-linked using a multivalent ion.
21. A hydrogel as claimed in claim 25 wherein the multivalent ion is calcium.

22. A hydrogel as claimed in claim 20 or 21 wherein the polymer having carboxylic acid groups is N-vinylpyrrolidone acrylic acid.
23. A hydrogel as claimed in any one of claims 1 to 22 additionally comprising a cross-linked form of at least one water soluble polysaccharide selected from
- (iii) pectin, pectic acid or pectate.
24. A hydrogel as claimed in claim 23 wherein the polysaccharide (iii) is cross-linked with a multivalent cation.
25. A hydrogel as claimed in claim 24 wherein the multivalent cation is calcium.
26. A hydrogel as claimed in claim 24 or 25 comprising 2 to 4% w/v of polysaccharide (iii) cross-linked by up to 0.2% w/v of the multivalent cation.
27. A hydrogel as claimed in any one of claims 1 to 26 incorporating a polyhydric alcohol to improve the shelf-life of the gel.
28. A hydrogel as claimed in claim 27 wherein the polyhydric alcohol is present in an amount up to 20% w/v of the hydrogel.

29. A hydrogel as claimed in claim 27 or 28 wherein the polyhydric alcohol is propylene glycol.

1-6

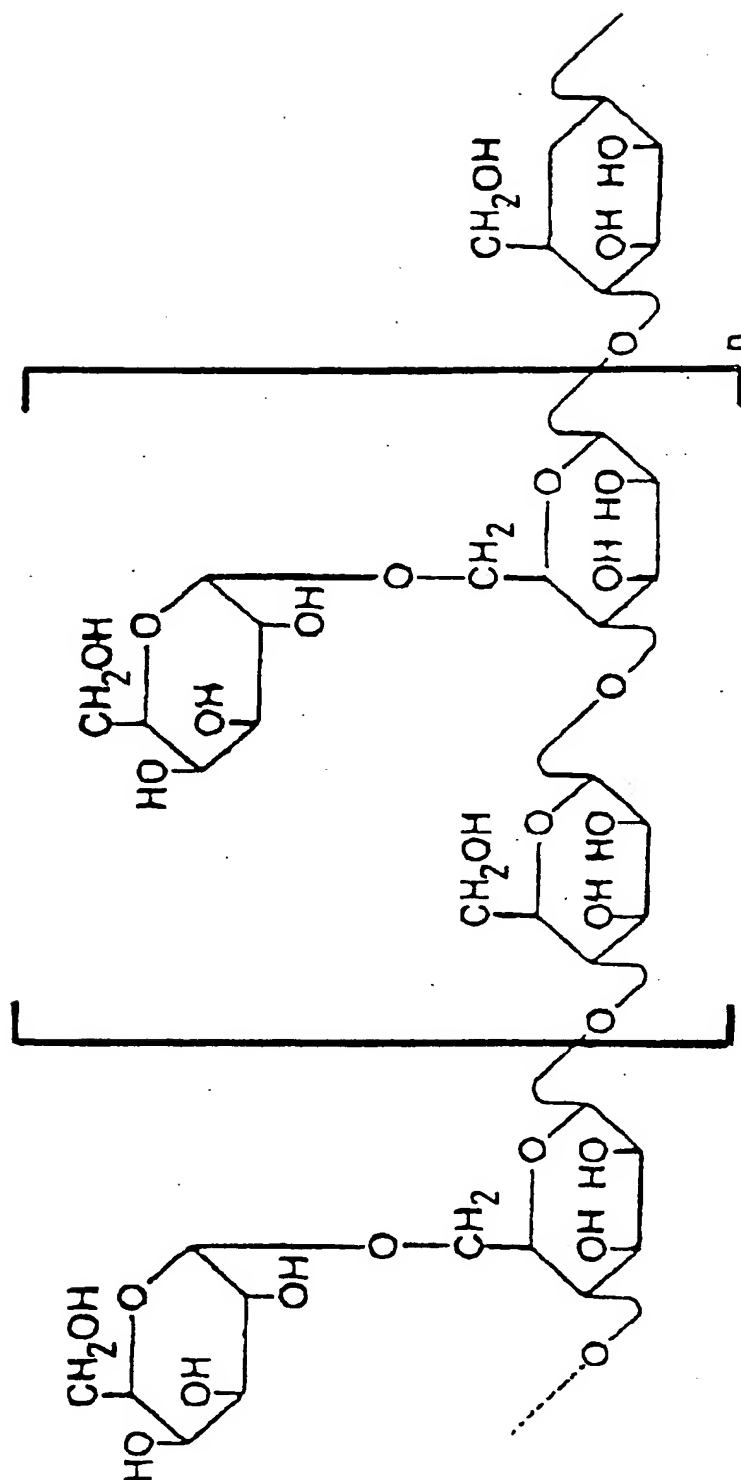


FIG. 1

2-6

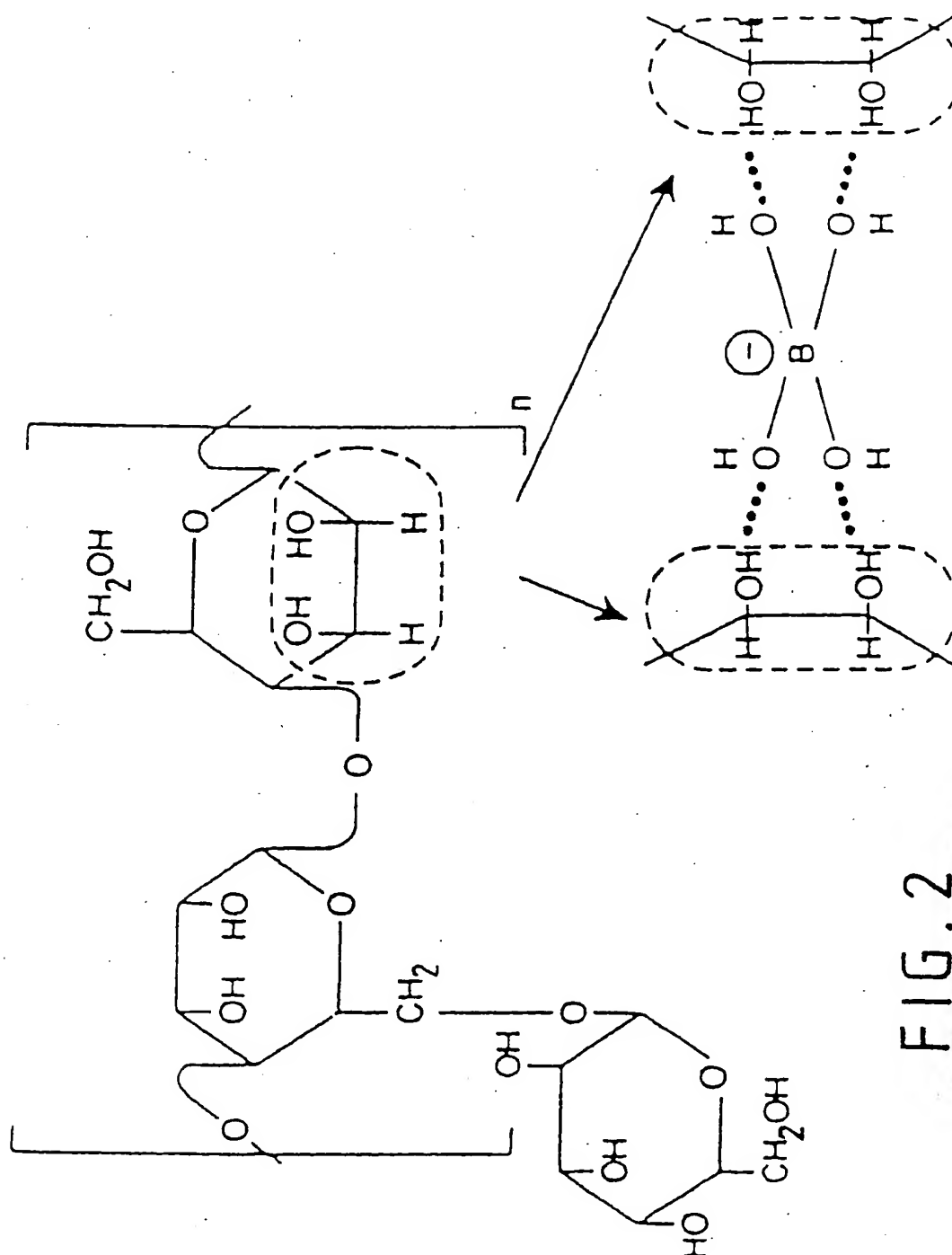
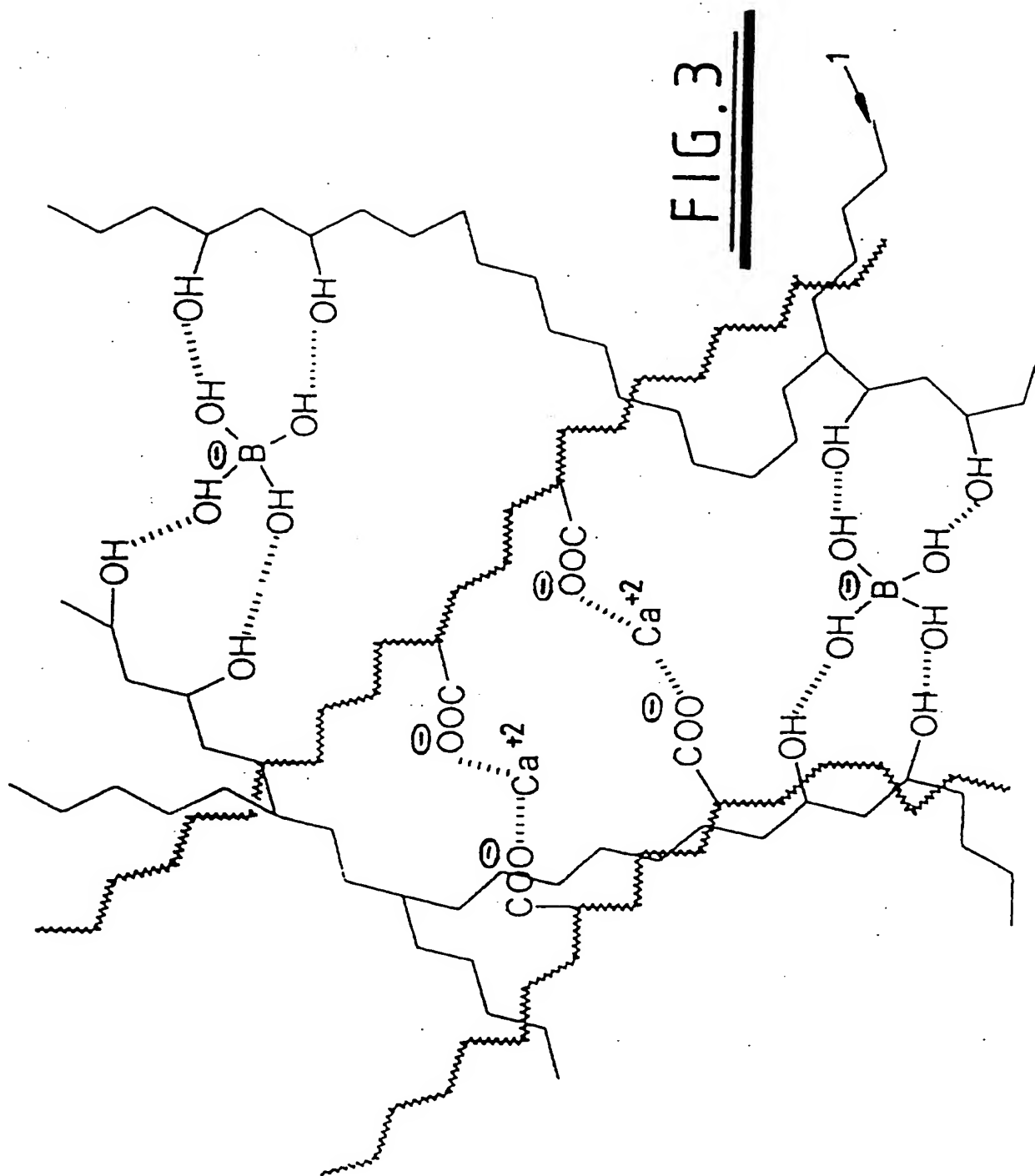
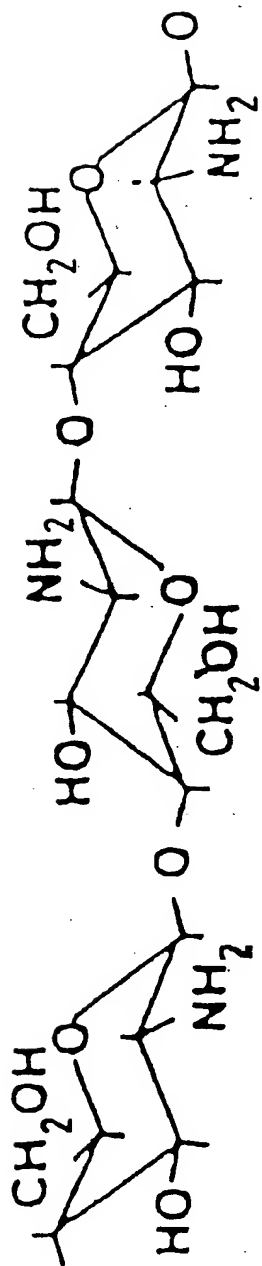
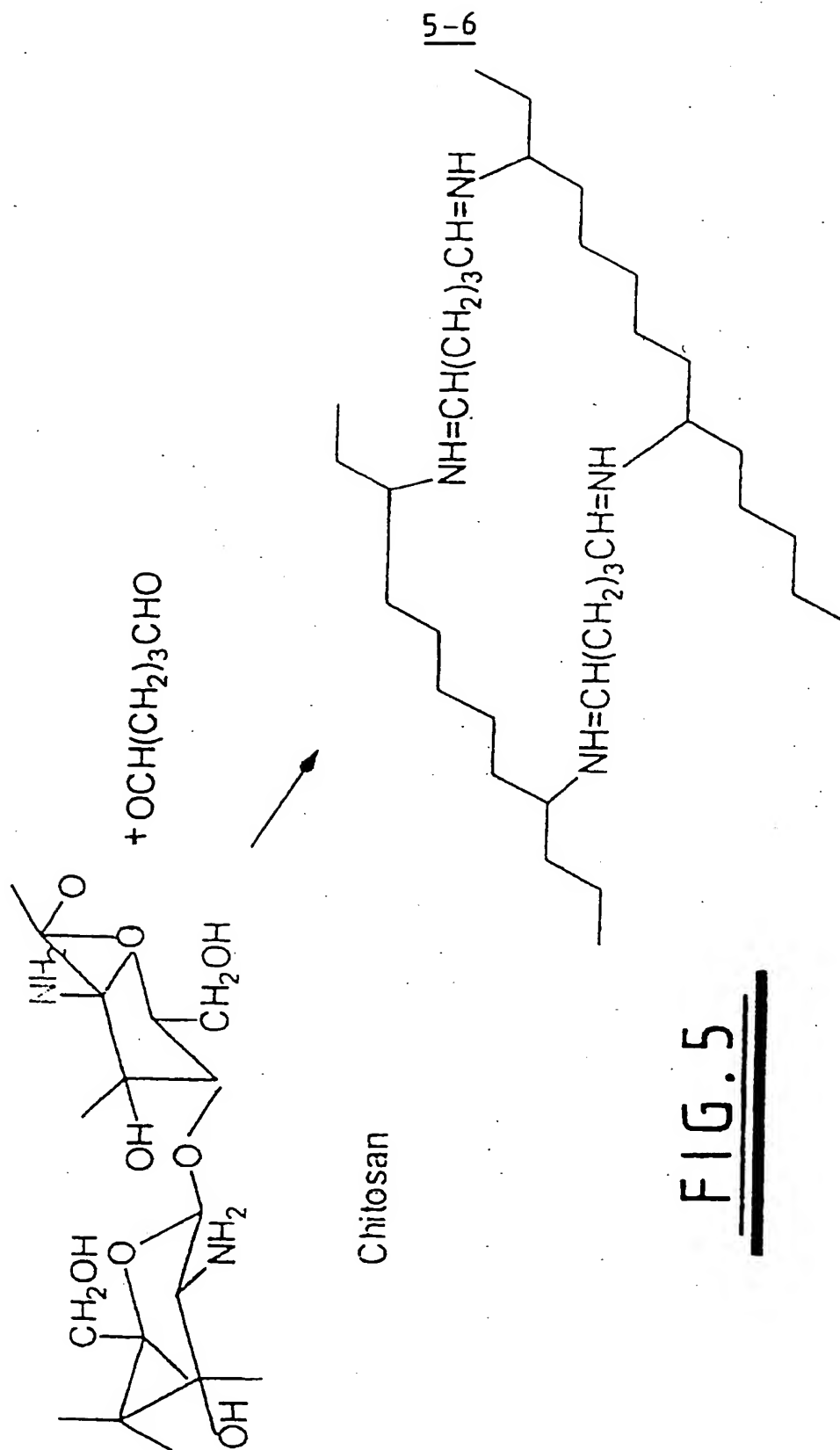
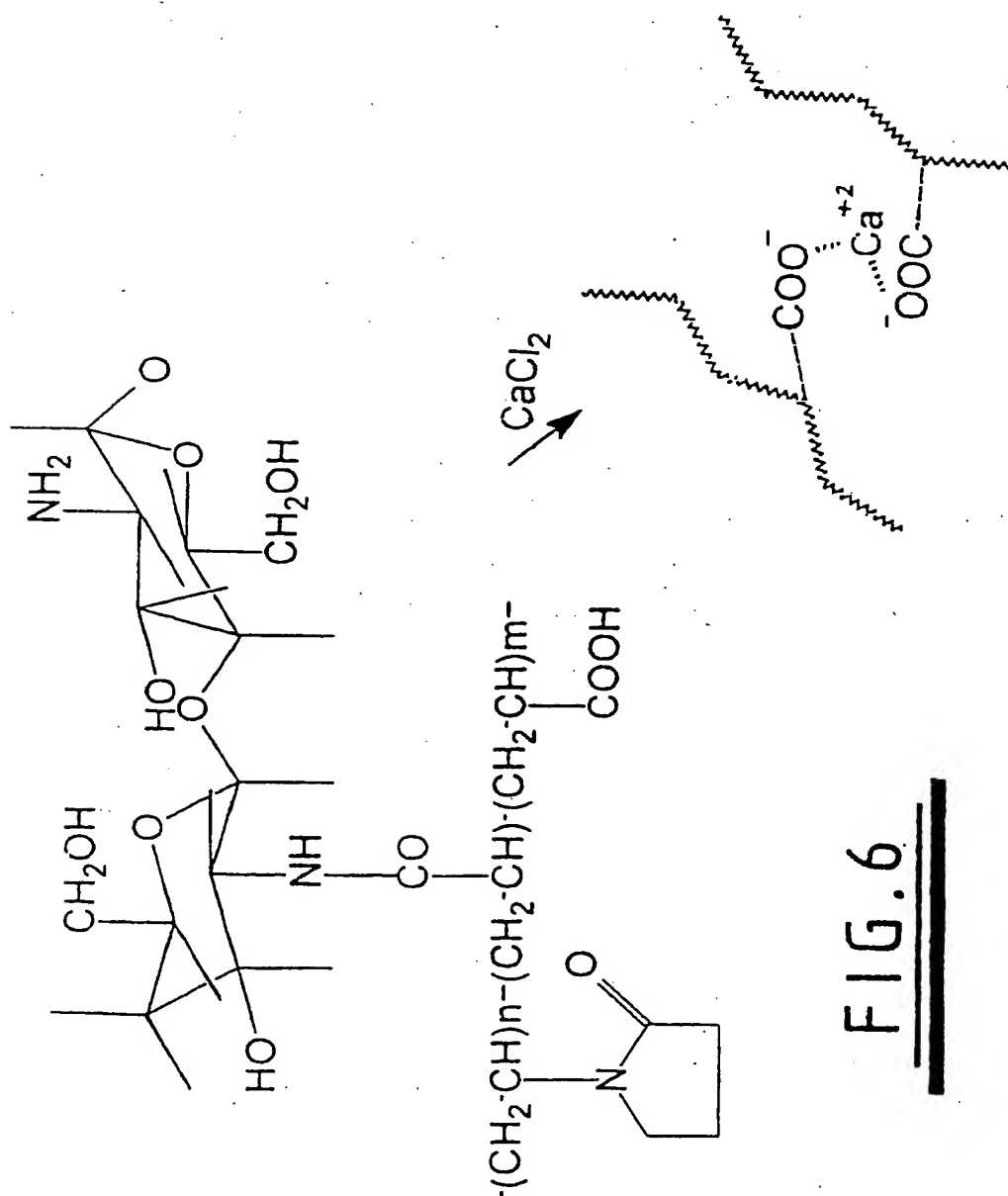


FIG. 2

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4-6FIG. 4

**FIG. 5**

6-6**FIG. 6**

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